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Authors' Response

'Kangaroo mother care' to prevent neonatal deaths due to pre-term birth complications

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We are writing in response to the letter by Sloan *et al.*¹ regarding our review of 'Kangaroo mother care'.² We are happy to see the ongoing interest in this publication and thank these colleagues for their letter. We fully agree that meta-analysis is frequently used inappropriately, especially given the ease of use of Revman[®] (Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The published paper was not such a 'quick and easy' meta-analysis, but developed through an extensive process for over 18 months with data kindly provided

by investigators, review at meetings of the Child Health Epidemiology Reference Group (CHERG) and by United Nations colleagues, as well as by external reviewers for the journal, including members of the Cochrane Collaboration.

We would again like to make it clear that this review is not intended to be a Cochrane review. As stated in the paper and in the introductory papers to the supplement, all the Lives Saved Tool (LiST) reviews follow a standard methodology developed by CHERG and WHO using GRADE criteria.³ The reviews are designed to inform inputs to LiST, which is a

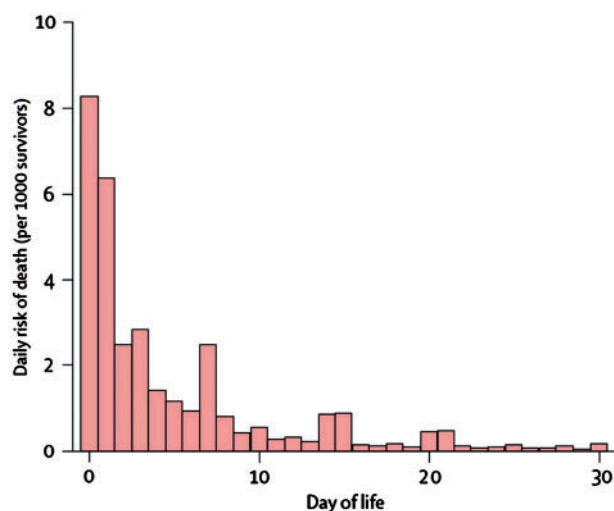


Figure 1 Daily risk of death during first month of life based on analysis of 47 DHS data sets (1995–2003) with 10 048 neonatal deaths. Deaths in first 24 h recorded as occurring on Day 0, or possibly Day 1, depending on interpretation of question and coding of response. Preference for reporting certain days (7, 14, 21 and 30) is apparent. Between 73 and 76% of neonatal deaths occur in the first 7 days after birth. Source: The Lancet.¹²

software tool designed to encourage evidence-based programme investment for mortality effect in a given country. The goal of this exercise is not to duplicate the work of the Cochrane collaboration, but to provide transparent estimates of the cause-specific mortality effects of priority interventions that are being scaled up in low- and middle-income countries. That said, it should be noted that the LiST review process identified limitations in previous Cochrane reviews. For example, the Cochrane review meta-analysis for Kangaroo mother care (KMC) combined mortality outcomes at 12 months, 6 months and pre-discharge.⁴ Any review is likely to have limitations and the goal for us all is to minimize these.

Intervention definition for RCT mortality meta-analysis

In the paper, we clearly defined, *a priori*, that for mortality outcomes we were examining the intervention of KMC commencing in the first week of life. Sloan *et al.* suggest that studies were excluded based on results. As stated in the paper, mortality studies were included or excluded based on explicit criteria—recruitment of babies with birth weight ≤ 2000 g and on their median day of initiating KMC (Figure 1 and Table 1 in the original article²). We did not use terms mentioned in her letter such as ‘early KMC’ and ‘traditional KMC’, as these may mean different things to different expert groups—we preferred a specific, reproducible measure regarding median day of

initiation of KMC. We included studies in which the median day of KMC initiation was ≤ 7 (Charpak,⁵ 4 days; Suman,⁶ 3.7 days; Worku,⁷ <1 day) and we excluded those studies in which the median day of KMC initiation was >7 days (Sloan *et al.*,⁸ 12.4 days; Cattaneo *et al.*,⁹ 10 days). We also excluded the more recent Sloan study from Bangladesh¹⁰ since birth weight was not measured for most neonates in the study, and there were other limitations in implementing this trial in a challenging setting in rural Bangladesh as discussed in the paper and as noted in Sloan *et al.*’s communication now. In the paper, we reported a sensitivity analysis including the two late initiation studies in the meta-analysis (Sloan *et al.*⁸ and Cattaneo *et al.*⁹). The mortality result remained significant {relative risk (RR) 0.64 [95% confidence interval (CI) 0.42–0.96]}.²

The reason for excluding studies of KMC starting after the first week of life is that the mortality effect of any intervention starting after the first week could not be compared with those starting in the first week since 75% of neonatal deaths occur in the first week. Sloan suggests that the distribution of neonatal mortality by day is ‘extremely variable’. However, the proportion of neonatal deaths that occur in the first week is actually remarkably stable in both Vital Registration¹¹ and Household Survey data¹² (Figure 1). Even with data limitations such as age heaping on Day 7 and misclassification of Day 0, there is a predictable distribution.¹³ We even considered a cut-off before the first week of life because $\sim 50\%$ of deaths occur in the first 48 h, and $>75\%$ occur in the first week. However, we applied a conservative and clear cut-off for median commencement of KMC by day 7.

We do not accept that studies were selected based on their results. They were selected on explicit, preset criteria, which in this case related to the usual PICO format of Patient, Intervention Comparison Outcome.

Outcome definition for RCT mortality meta-analysis

Our review focused on ‘neonatal’ mortality, which differs from the earlier Cochrane review (Conde Aguedelo 2003)⁴ in which the mortality meta-analysis combined infant mortality,⁵ 6-month mortality⁸ and pre-discharge mortality.⁹ Both Charpak and Suman kindly provided us with their unpublished neonatal mortality data. The Worku trial⁷ was based on pre-discharge neonatal mortality and we recognized this as a limitation and discussed this in the text and the detailed GRADE webtable marks down the quality based on this and other limitations. Although some post-discharge neonatal deaths may have been missed, given the steep survival curve, such deaths are likely to have been a small proportion and given the expectation of fewer deaths in the KMC

group this loss to follow-up bias will be expected to weaken the effect size and is conservative. In the Suman trial,⁶ where cases were followed after discharge, no further neonatal deaths were identified post-discharge in control or intervention arms.

We do not agree with Sloan *et al.*'s point that it is incorrect to undertake meta-analysis of trials for an outcome (in this instance neonatal mortality) that those trials were not individually powered to examine. Indeed, we would argue that one of the most important uses of meta-analysis is precisely for such situations.

Neither do we accept their argument that these studies are too heterogeneous to be combined. We followed standard meta-analysis rules to examine for heterogeneity using the I^2 statistic as laid out in our methods section under the subtitle 'Analyses, and summary measures'. For these three RCTs, the $I^2=0.0\%$, $P=0.539$ and so a fixed effects meta-analysis was appropriate. Mantel-Haenszel weights were used to combine the studies. The weight given to Worku simply reflects lower standard error in their estimates, as shown by the narrower confidence interval. This is the standard approach to weighting. No special weighting was applied.

Mortality outcome observational study meta-analysis

Sloan *et al.* state that a meta-analysis of observational studies 'is almost a contradiction in terms' and should not be done. Once again we emphasize that this review is not a Cochrane review—our purpose is to examine the data to inform implementation at scale. As stated in the paper, the purpose was to examine whether the effect estimate obtained from small, RCTs measuring efficacy would be consistent with the effect estimate obtained from larger, observational studies with weaker designs. The paper explicitly allocates these observational studies a low level of evidence. This meta-analysis is of relevance to programmatic planners since the results suggest that wide-scale, routine implementation of KMC is still associated with considerable mortality reduction of around 32% reduction in deaths for babies under 2000 gms.

Morbidity outcome RCT meta-analysis

We agree that our paper should have had more detailed discussion of the inputs for the morbidity meta-analysis compared with the mortality analysis. The reported morbidity outcomes in most of these trials are beyond the neonatal period and morbidity, notably infections in pre-term infants tends to peak later than mortality. The paper presented a

meta-analysis with studies of both early and late initiation of KMC [RR 0.34 (95% CI 0.17–0.65)].² We should also have reported a meta-analysis excluding the KMC studies with later initiation as per the criteria set out for the mortality RCT meta-analysis. The results of this analysis are not very different in terms of the point estimate [RR 0.25 (95% CI 0.06–1.07)].

Weight cut-off of <2000 g

We state in the paper which of the studies included had a weight cut-off of ≤ 2000 g. A lower cut-off will dilute the effect in the morbidity meta-analysis (Udani,¹⁴ 1800 g) and the observational study meta-analysis (Kambarini,¹⁵ 1600 g and Lincetto,¹⁶ 1800 g) as smaller babies have a higher risk, and hence this bias is conservative. The exclusion of babies <1000 g in Pattinson *et al.* may increase the effect in the observational meta-analysis in the observational study meta-analysis. However, these biases are discussed in the paper and none of these effect sizes is being used in LiST—the analysis for morbidity and observational trials was to examine consistency of effect between these studies and the RCT meta-analysis.

Misinterpretation of study statistics

Finally we were surprised to read the section entitled 'Misinterpretation of study statistics', which refers to an e-mail notice regarding the paper circulated by others.¹ This e-mail suggested that KMC could halve all neonatal deaths, instead of halving of neonatal deaths in stable neonates <2000 g as we clearly stated in the paper. Such e-mails are, unfortunately, beyond our control, and do not seem appropriate material for a journal letter.

Conclusions

Sloan *et al.* agree with our statement that there is insufficient evidence to recommend community initiation of KMC.¹ Although Sloan *et al.* state that KMC, especially started early '...has potential for averting some neonatal mortality associated with prematurity...', their conclusion is that there is 'no single adequately designed and implemented trial to demonstrate the effect of early KMC on newborn or infant mortality', even for facility-based KMC. We all agree more trials are needed, especially for community initiation, and we all agree future trials should learn from the limitations of the ones included and excluded here. We also all agree that there is as yet no one 'perfect' trial even for facility KMC, and as stated in our paper, all of the three RCTs in our

meta-analysis have limitations. However, we do not agree with Sloan *et al.* that policy and programme investment in facility KMC should wait for a 'perfect' trial. We, and the many scientists who reviewed this paper, believe that this review is transparent in providing a mortality effect size of KMC and in discussing the potential biases in both directions. Indeed, many of the biases are likely to result in underestimation of effect for the real question for public health relevance—namely, how much better is KMC than no care at all.

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